Preliminary Report of a Nationwide Case-Control Study for Identifying Risk Factors of Tuberculosis Following Renal Transplantation

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ABSTRACT

Background. Tuberculosis (TB) is an important infection encountered posttransplantation, especially among patients in developing countries, where there are high incidences of morbidity and mortality.

Materials and Methods. One hundred and twenty subjects (1%) from 15 major kidney transplantation centers in Iran from 1984 to 2003 were compared with 440 controls who were matched for operative time, treatment center, and surgical team.

Results. Mean ages of research subjects and controls were 38.6 and 36.6 years ($P = .04$), respectively. The mean duration of pretransplantation hemodialysis was 29 months (range, 2 to 192 months) in research subjects and 20 months (range, 1 to 180 months) in controls ($P = .003$). Positive past history of tuberculosis was detected in 4 (3.3%) research subjects and in 7 (1.5%) controls ($P = .2$). Fifty-two research subjects (43.3%) and 241 controls (54.8%) had pretransplantation purified protein derivative of tuberculin less than 5 mm ($P = .02$). Mean dosages of initial and maintenance immunosuppressive drugs in research subjects and in controls were not significantly different. Sixty research subjects (50%) and 152 controls (34.5%) had rejection prior to diagnosis of TB ($P = .03$).

Conclusion. To our knowledge, this is the first study that demonstrates an increased risk of posttransplant TB by prolonged duration of pretransplant hemodialysis and number of posttransplant rejection episodes. Further study is needed to clarify these findings specifically with respect to various immunosuppressive regimens.

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TUBERCULOSIS (TB) is an uncommon infectious complication after kidney transplantation and may jeopardize the function of the renal allograft. Both primary infection and reactivation of *Mycobacterium tuberculosis* (mt) infection in kidney transplant patients are common therapeutic problems, especially in those receiving multiple immunosuppressive drugs in developing countries.

Reactivation of dormant infection is the usual mode of acquisition, and nosocomial transmission occurs infrequently. Donor-transmitted extrapulmonary infection has been reported.[1] Additionally, tuberculous nephropathy[2] and granulomatous interstitial nephritis[3] involving recipients have been described.

Immunosuppression assists reactivation of latent tuberculosis or progression of acquired disease in kidney transplant recipients.[4,5] Apart from the usual pulmonary presentations, hematogenous spread of tuberculosis frequently occurs in these cases,[6] affecting joints or bone marrow,[7] nervous system,[8,9] and the kidney allograft.[4] These extrapulmonary manifestations as well may lead to a delay in the diagnosis and, therefore, enhanced morbidity and mortality of kidney recipients.

Most previous studies on posttransplant TB are case reports and case series. Probable risk factors for TB have not been compared with a control population of renal transplant recipients. The present study was undertaken to determine the clinical manifestations and laboratory findings of TB in renal transplant patients, as well as the potential risk factors for this disease following transplantation. To our knowledge, this is the first countrywide, case-control study on TB following renal transplantation.

MATERIALS AND METHODS

This case-control study was carried out at 15 university teaching hospitals. The hospital records and reports of outpatient follow-up visits of 12,820 patients who received a kidney transplant between 1984 and 2003 were reviewed. In addition, we interviewed the nephrologists who were responsible for visiting all 120 patients with the diagnosis of posttransplant TB. We selected 440 patient controls who were transplanted at the same time by the same surgical team. In our study, all kidneys were harvested from living donors.

Clinical charts and hospital records were reviewed for confirm TB according to our diagnostic criteria, demographic information, degree of immunosuppression, pre- and posttransplantation reaction to purified protein derivative of tuberculin (PPD), previous history of tuberculosis, time to development of tuberculosis, clinical presentation, laboratory data, radiographic and pathological features, sites of involvement, methods for diagnosis, treatment protocol, and number of rejection episodes prior to tuberculosis.

According to WHO recommendations, case detection and treatment of TB in our country is performed under a strategy of direct observed treatment, short course; therefore, "Once patients with infectious TB (bacilli visible in a sputum smear) have been identified using microscopy services, health and community workers or trained volunteers observe patients swallowing the full course of the correct dosage of anti-TB medicines."[10]

The diagnosis of tuberculosis was considered certain in symptomatic patients if *Mycobacterium tuberculosis* was cultured from any clinical sample, acid-fast bacilli were seen on smear, polymerase chain reaction was positive for *M tuberculosis,* and granuloma with caseating changes as well as acid-fast bacilli were found on histopathology. In our national health system, the Ziehl-Neelsen stain method is routinely used for staining; and all patients receive isoniazid (INH), rifampin (RMP), pyrazinamide, and ethambutol for the first 2 months, and INH and RMP for the subsequent 4 months.

TB was considered probable in patients whose radiographic and nonspecific laboratory data were supportive of a diagnosis of TB and whose clinical pictures were highly suggestive of tuberculosis that resolved with specific antituberculous treatment.

Cyclosporine (CsA), azathioprine, and steroids were used during the study period by the majority of centers. After 1990, the majority of patients received mycophenolate mofetil instead of azathioprine. Doses of CsA were adjusted to obtain trough plasma levels of 200 to 400 ng/mL (as determined by radioimmunoassay) during the first month and 100 to 200 ng/mL thereafter. Rejection episodes were usually treated with boluses of steroids; cases of steroid-resistant rejection, received antilymphocyte antibodies-antilymphocyte globulin, antithymocyte globulin (ATG), or OKT3. Since 1985, pretransplantation HIV screening has been performed routinely in all centers. A positive response to tuberculin (PPD) test was defined as an induration of 5 mm or more in diameter at 48 to 72 hours after administration of five tuberculin units.

We compared the demographic characteristics and clinical and laboratory variables between control group and kidney transplant recipients with TB. All statistical associations were analyzed using either the Mann-Whitney or a two-tailed t tests for quantitative variables and the chi-square or Fisher's exact test for qualitative variables. P values greater than .05 were considered statistically significant. We calculated odds ratios for all risk factors evaluated in this study.

RESULTS

Among patients who had received a kidney transplant in 15 university teaching hospitals from different geographic areas in Iran between 1984 and 2003, 120 (1%) developed tuberculosis. Clinical findings and main comparisons between cases and controls are given in Tables 1 and 2, respectively.

All patients in both groups received prednisolone at similar mean doses (1.5 vs 1.9 mg/kg, $P = .5$; odds ratio [OR] = 1.2; 95% confidence interval [$Cl_{95\%}$] = 0.7 to 2). Twenty-three patients in the study group (19.2%) and 73 subjects in the control group (16.6%) received MMF ($P = .3$) with similar mean doses (19.5 mg/kg vs 19.25 mg/kg, $P = .5$). CsA was prescribed in 113 cases (94.2%) and 412 controls (93.6%, $P = .5$) at identical mean doses (both 3.8 mg/kg).

Table 1. Clinical Findings of Research Subjects and Controls

Symptom	Subject (%)	Control (%)	P value
Cough*	59 (49.2)	1 (0.2)	.00
Sputum production	55 (45.8)	1 (0.2)	.00
Fever	94 (78.3)	2 (0.5)	.00
Night sweating	40 (33.3)	1 (0.2)	.00
Weight loss	40 (33.3)	0	.00
Hemoptysis	13 (10.8)	0	.00

*Cough: >3 weeks cough.

Table 2. Clinical Characteristics of Kidney Transplant Recipients With Tuberculosis Compared With Controls

Variable	Subject (n = 120)	Control (n = 440)	P value	OR
Mean age, year (range)	38.6 (1–71)	36.6 (8–67)	.04*	
Sex (M/F)	62/58	242/198	.5	0.87 $CI_{95\%}$: 0.58–1.3
Weight	56.1 (26–96)	57.2 (18–92)	.5	
Living in rural areas	14 (11.5%)	50 (12%)	.8	0.96, $CI_{95\%}$: 0.5–1.8
Type of tuberculosis				
Pulmonary	82 (68.3%)			
Extrapulmonary	29 (24.2%)			
Disseminated	9 (7.5%)			
History of prior renal transplantation	6 (5.2%)	21 (5.1%)	.9	0.95, $CI_{95\%}$: 0.37–2.4
Rejection prior to diagnosis of TB	60 (50%)	152 (34.5%)	.03	
One episode	32 (26.7%)	111 (25.2%)		
Two episodes	16 (13.3%)	26 (5.9%)		1.89, $CI_{95\%}$: 1.23–2.91
Three episodes	7 (5.8%)	7 (1.6%)		
Four episodes	2 (1.7%)	7 (1.6%)		
Five episodes	3 (2.5%)	1 (0.2%)		
History of tuberculosis				
In patient	4 (3.3%)	7 (1.5%)	.2	2.13, $CI_{95\%}$: 0.5–8.28
In first relatives	9 (7.5%)	17 (3.8%)	.15	2.02, $CI_{95\%}$: 0.8–4.95
Mean time (mo) of being on hemodialysis prior to transplantation	29 (2–192)	20 (1–180)	.003*	

*Mann-Whitney U test.

Ninety-three study patients (77.5%) and 341 controls (77.1%, P = .5) received azathioprine at identical mean doses (1.7 mg/kg). According to our protocol, all patients with rejection received pulses of methylprednisolone (and rarely ATG if needed—one case in each group, 0.8% vs 0.2%) or ALG one case and seven controls, 0.8% vs 1.6%, P = .4; OR = 1.9, $CI_{95\%}$ = 0.2 to 15.8).

No patient was positive for HIV in this study. Seventy-seven study patients (64.2%) and 1 patient (0.2%) in the control group had radiological evidence compatible with tuberculosis (P = .0). Table 3 shows the main radiographic findings of study patients and controls.

Six study patients (9%) and six controls (3.1%) had a history of TB and of receiving anti-TB medicines (P = .06). Fifty-two study subjects (43.3%) and 241 controls (54.8%) had pretransplantation PPD values less than 5 mm (P = .02). In addition, if we change the cutoff point of PPD to 10 mm, 48 study subjects (40%) and 221 subjects in the control group (50.2%) had pretransplantation PPD levels less than 10 mm (P = .05). Mean time to diagnosis of TB was 15.7 months (range, 1 to 110 months) after transplantation.

Table 3. Radiological Features of Chest X-ray in Cases and Controls

Controls (%)	Subjects (%)	Feature
1 (0.2)	44 (57.2)	Apical infiltration and calcification
	17 (22)	Pleural effusion
	7 (9.1)	Apical cavitations
	9 (11.7)	Miliary pattern
1	77	Total

DISCUSSION

Infection caused by *M tuberculosis* is noticeable among the general population in Iran.[11] Moreover, this microorganism is clearly a potential pathogen in kidney transplant recipients.[12] TB may present as pulmonary, extrapulmonary, or disseminated disease during the posttransplantation period. The increasing global incidence of tuberculosis during the past decade[13] has revealed the demand to clarify screening methods, to have a high index of suspicion, and to begin isoniazid chemoprophylaxis in recipients at high risk for reactivation of latent infection.

The risk factors for tuberculosis in transplant patients are as yet poorly defined, although the role of intensified immunosuppression for a failing graft appears to be important. Although our study had some limitations, to our best knowledge, it is the first comparative case-control study.

Although older people are relatively immunocompromised, the mean age of persons with TB was similar to the control group in our study, showing that age, per se, may not be an independent risk factor. Similarly, although male subjects may be more prone to TB in the general population, TB was seen with the same frequency in men and women in our study. Therefore, the role of other risk factors and immunosuppression seems to be more of a determining factor.

In fact, the degree of immunosuppression in our research patients was not higher than that recognized for the control group, all recipients received the same immunosuppressive drugs following transplantation. On the other hand, our data agreed with the hypothesis proposed by some researchers that administration of antilymphocyte antibodies

enhances the risk of tuberculosis dissemination.[7,14] Because a history of graft rejection and the use of antilymphocyte globulins was present more frequently among study compared with control subjects, our findings support the role of these compounds as potential risk factors for developing TB. Although coadministration of CsA and rifampin may decrease CsA levels in kidney transplantation recipients, this study was not designed to identify the significance of this drug interaction and its consequences.

In this study, we found that a longer history of hemodialysis was associated with posttransplant TB compared with controls. To our knowledge, this is the first report demonstrating an effect of long-term hemodialysis prior to transplantation on the development of posttransplantation TB. Because the degree of immunosuppression is enhanced with increased durations of hemodialysis, this interval may enhance the probability of posttransplantation TB.

Prevention of TB in kidney transplantation is a complicated issue. Owing to the underlying hemodialysis and end-stage renal disease prior to transplantation, patients are usually immune compromised, thereby making pretransplant screening using a PPD test unhelpful. This may be why preoperative PPD skin tests and delayed-type hypersensitivity reactions are not generally accepted. Our findings revealed a lower reaction to PPD among our study subjects compared with controls. Because decision making on initiating INH chemoprophylaxis is usually based on a PPD skin test, one may extrapolate that a smaller number of study compared with control subjects may have received INH prior to transplantation. Because of a high risk of hepatotoxicity, chemoprophylaxis in renal transplant recipients is controversial. Even in countries with a high incidence of tuberculosis,[15,16] the common trend in the published reports is toward avoiding the use of INH. Although INH prophylaxis was indicated in nearly half of our subjects, a low percentage of patients received this drug in our study. There is a controversy regarding the cutoff point for PPD reactions to initiate chemoprophylaxis among specialists working in kidney transplantation in our country.

According to our national guidelines, all candidates for transplantation with a PPD greater 5 mm receive INH prophylaxis. INH prophylaxis may be worthy of being recommended in transplant recipients with positive PPD reactions. Considering the frequency of TB in kidney recipients—3 times that of recipients with negative PPD tests[7,8]—the American Thoracic Society suggests use of INH in PPD-positive allograft recipients with previous pulmonary tuberculosis.[17] On the other hand, considering the elevated risk of hepatotoxicity, some researchers recommend that regular administration of INH may have a deleterious effect on a patient's condition.[18]

It would be worthwhile to know whether a recipient with a negative tuberculin test who received an organ from a PPD-positive donor[7] needs chemoprophylaxis. There are no data addressing prophylaxis in this condition; future studies should examine this question.

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